UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/581,773	02/12/2007	Hans J. Stauss	28646/42100	7037

4743 7590 01/04/2010

MARSHALL, GERSTEIN & BORUN LLP
233 SOUTH WACKER DRIVE
6300 SEARS TOWER
CHICAGO, IL 60606-6357

EXAMINER	
SKELDING, ZACHARY S	
ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
01/04/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/581,773	STAUSS ET AL.	
	Examiner	Art Unit	
	ZACHARY SKELDING	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *1-11 and 20-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-16* is/are rejected.

7)☒ Claim(s) *17-19* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 June 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11-17-06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election with traverse of Group II in the reply filed October 1, 2009 is acknowledged.

   The traversal is on the ground(s) that (1) at least Groups II and III should be examined together and (2) Stanislawski does not demonstrate that the claimed inventions lack unity over the art.

   The first argument is found persuasive upon further consideration and in view of applicant's argument and thus Groups II and III will be rejoined and examined together.

   The later argument is not found persuasive essentially for the reasons of record. In particular, applicant's argument focuses on the specificity of the Stanislawski TCR for the MDM2 antigen and not the WT1 antigen and yet the claimed invention includes, for example, "any novel method of combating cancer as herein described" which as put forth in the restriction requirement mailed April 1, 2009 includes : "…therapeutically useful molecules, in particular to T cell receptors (TCRs) which may be introduced into a patient's own T cells in order to direct the T cells to kill cancer cells within the patient, particularly cancer cells which express the Wilms Tumour antigen-1 (WTI)." Notably this disclosure of the instant specification is not limited only to targeting the WT1 antigen, per se.

   The requirement as to Groups I, (II and III), IV, V and VI is still deemed proper and is therefore made FINAL.

   Therefore, claims 12-19 are under examination.

   Claims 1-11 and 20-27 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Group, there being no allowable generic or linking claim.

   Applicant timely traversed the restriction (election) requirement in the reply filed on October 1, 2009.

2. The specification is objected to because it contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reason(s): the specification is replete with sequences that fall within the ambit of 37 CFR 1.821(a)(1) and (a)(2) which lack a "SEQ ID NO:" identifier (see, e.g.., page 5). Moreover, it is noted that the "Schedule of SEQ ID NOs." on page 17 is not sufficient to fully identify these sequences as required by the rules. Rather, each occurrence of a polynucleotide or polypeptide sequence as defined by the rules must be accompanied by the identifier "SEQ ID NO: __" Applicant is further reminded that

sequences appearing in Figures are also subject to the sequence rules. Appropriate correction is required.

3. The claims are objected to because they contain sequences not appropriately identified with a "SEQ ID NO:" identifier. Appropriate correction is required.

4. Claims 17-19 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from another multiple dependent claim. See MPEP § 608.01(n). Accordingly, these claims have not been further treated on their merits.

5. Claims 15 and 16 are objected to because a claim cannot depend on itself.

6. 35 U.S.C. §101 states:

   Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

7. Claims 12-16 are rejected under 35 USC §101 because the claimed invention is directed to non-statutory subject matter.

   Claims 12-16 recite "polynucleotides" that do not sufficiently distinguish over the product that exists naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. *See Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "isolated" or "purified". See MPEP 2105.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

   The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 12 and 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

   On the one hand claims 12 and 13 could be interpreted as claims where the language "encoding the alpha/beta chain portion as defined in claim 1" is shorthand for something like "a polynucleotide encoding a TCR alpha chain portion containing three complementarity determining regions (CDRs): CDR1.alpha.: SSYSPS CDR2.alpha.: YTSAATL CDR3.alpha.: VVSPFSGGGADGLT or comprising or consisting of SPFSGGGADGLT."

On the other hand claims 12 and 13 could be interpreted as claims where the language "encoding the alpha/beta chain portion as defined in claim 1" is shorthand for something like "a polynucleotide encoding a TCR molecule containing an alpha chain portion and a beta chain portion wherein the alpha chain portion comprises three complementarity determining regions (CDRs): CDR1.alpha.: SSYSPS CDR2.alpha.: YTSAATL CDR3.alpha.: VVSPFSGGGADGLT or comprising or consisting of SPFSGGGADGLT."

These interpretations are very different, indeed, they are mutually exclusive because by the first interpretation the claims encompass a polynucleotide encoding only a TCR alpha OR beta chain portion while the second interpretation is that the claims encompass the genus of polynucleotides encoding an alpha or beta chain with the CDRs explicitly recited in claim 1 and further encoding a cognate generic TCR alpha or beta chain not structurally defined by the claims.

Thus, the instant claims fail to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 12-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polynucleotide that encodes a TCR alpha chain derived from a TCR which specifically binds the peptide RMFPNAPYL bound to an HLA-A2 class I molecule, wherein said TCR alpha chain comprises three complementarity determining regions (CDRs): CDR1.alpha.: SSYSPS, CDR2.alpha.: YTSAATL, and CDR3.alpha.:, wherein said CDR3.alpha. is VVSPFSGGGADGLT or wherein said CDR3.alpha. is SPFSGGGADGLT;

or for an isolated polynucleotide that encodes a TCR beta chain derived from a TCR which specifically binds the peptide RMFPNAPYL bound to an HLA-A2 class I molecule, wherein said TCR beta chain comprises three complementarity determining regions (CDRs): CDR1.beta.: DFQATT, CDR2.beta.: SNEGSKA, and CDR3.beta.:, wherein said CDR3.beta. is SARDGGEG or wherein said CDR3.beta. is RDGGEGSETQY;

or for an isolated polynucleotide that encodes a single chain TCR which specifically binds the peptide RMFPNAPYL bound to an HLA-A2 class I molecule, wherein said single chain TCR contains an alpha chain portion and a beta chain portion, said alpha chain portion comprising three complementarity determining regions (CDRs): CDR1.alpha.: SSYSPS, CDR2.alpha.: YTSAATL, and CDR3.alpha.:, wherein said CDR3.alpha. is VVSPFSGGGADGLT or wherein said CDR3.alpha. is SPFSGGGADGLT, and said beta chain portion comprising three complementarity determining regions (CDRs): CDR1.beta.:

DFQATT, CDR2.beta.: SNEGSKA, and CDR3.beta.:, wherein said CDR3.beta. is SARDGGEG or wherein said CDR3.beta. is RDGGEGSETQY;

does not reasonably provide enablement for the claimed invention which encompasses in its breadth nucleic acids encoding TCRs based on the particular CDR sequences recited in claim 1 but having up to three residues in one or more CDR replaced by another amino acid residue. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

As is well known to the skilled artisan, T-cell receptors (TCRs) are membrane anchored heterodimers structurally related to antibody molecules (see, e.g., applicant's remarks filed October 1, 2009 at page 3, 1st paragraph). Since TCRs and antibodies are structurally related, teachings regarding antibody structure-function will be considered to apply to the structure-function of TCRs as well.

The instant specification discloses a single TCR which specifically binds the peptide RMFPNAPYL bound to an HLA-A2 class I molecule. (see pages 18-19). The instant specification further discloses how to make CDR variants in general, but provides no specific guidance about how to make variants of the single disclosed TCR (see, e.g., page 7, 1st paragraph).

However, neither the teachings of the instant specification nor the knowledge in the art are sufficient to make the breadth of TCRs encompasses by the instant claims.

This is because even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function (see, e.g., Rudikoff et al., Proc. Natl. Acad. Sci. USA, 79:1979-1983, March 1982). Rudikoff teaches that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. Similarly, Colman P. M. (Research in Immunology, 145:33-36, 1994) teaches that even a very conservative substitution may abolish binding or may have very little effect on the binding affinity (see pg. 35, top of left column and pg. 33, right column).

To further illustrate the level of experimentation required to generate the TCR encompassed by the breadth of the instant claims, consider Vajdos et al. (J Mol Biol. 2002 Jul 5;320(2):415-28) which teaches "[t]he specificity and affinity of an antibody for its cognate antigen is determined by the sequence and structure of the variable fragment (Fv): a heterodimer consisting of the N-terminal domains of the heavy and light chains. Even within the Fv, ***antigen binding is primarily mediated by the complementarity determining regions (CDRs), six hypervariable loops (three each in the heavy and light chains) which together present a large contiguous surface for potential antigen binding.*** Aside from the CDRs, the Fv also contains more highly conserved framework segments which connect the CDRs and are mainly involved in supporting the CDR loop conformations, although in some cases,

framework residues also contact antigen. As an important step to understanding how a particular antibody functions, it would be very useful to assess the contributions of each CDR side-chain to antigen binding, and in so doing, to produce a functional map of the antigen-binding site." (see, page 416, column bridging paragraph, emphasis added).

Vajdos goes on to teach that "[b]y analyzing panels of point mutants, a detailed map of the binding energetics can be obtained, but the process can be ***very laborious*** because ***individual mutant proteins must be made and analyzed separately.*** In particular, ***a comprehensive analysis*** of an antigen binding site would ideally ***encompass all CDR residues***, and this would require the analysis of dozens or even hundreds of point mutants." (see page 416, right column, first paragraph, emphasis added). Vajdos solution to this dilemma was to make use of a recently developed shotgun scanning mutagenesis which "uses phage displayed libraries of protein mutants constructed using degenerate codons with restricted diversity." While this "recently developed shotgun scanning mutagenesis" is an improvement over previous strategies as taught by Vajdos, it nonetheless requires extensive planning and analysis and involves the synthesis of 18 sets of degenerate oligonucleotides for the construction of the 4 phage libraries required to comprehensively scan the heterodimeric chains of the antibody (see, in particular, page 416, right column, 2nd paragraph and pages 425-427, Materials and Methods.)

Furthermore, even after performing this comprehensive scanning mutagenesis of all CDR residues from the particular anti-ErB2 antibody under study, Vajdos would still not have been able to say which CDR residues are actually involved in antigen binding, and which are involved in stabilizing the secondary and tertiary structure of the CDRs within the context of the heavy and light chains as a whole, without the structure of the unbound antigen-binding site of the antibody to aid in their analysis (see, in particular, Discussion, pages 422-425).

Rather, Vajdos needed to perform not only a comprehensive shotgun scanning mutagenesis of all CDR residues of the antibody under study but also needed a structure of the unbound antigen-binding site in hand to gain a sufficient understanding of the contribution of each CDR to antigen-binding that would be required to adequately predict which CDR residues can be mutated, and to what extent, or in what context of additional compensatory mutations in other regions of the antibody. Moreover, given an amino acid substitution that ablated binding, without the crystal structure in hand, still further experimentation would have been required to determine the flexibility in this particular residue, i.e., it's general tolerance or intolerance to change.

Thus, in view of the teachings of Rudikoff, Colman and Vajdos the instant specification does not provide sufficient guidance or direction to make the TCR molecules encompassed by the breadth of the instant claims. Rather, the instant claims encompass an invention of tremendous scope and essentially calls for trial and error by the skilled artisan using techniques known in the art to begin discovering the claimed invention without assisting the skilled artisan in such an endeavor, which is insufficient to constitute adequate enablement.

The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.
Thus, undue experimentation would be required to produce the claimed invention commensurate with the scope of the claims from the written disclosure alone. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 12-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., Vas-Cath, Inc., v. Mahurkar, 935 F.2d at 1563, 19 U.S.P.Q.2d at 1116.

In the instant case, the claims, given their broadest reasonable interpretation consistent with the instant specification read on polynucleotides enconding TCR alpha and/or beta chains with particular CDRs but the claims do not recite which antigen is bound by polypeptides encoded, for example by the single chain TCR polynucleotide. Other than binding to the peptide RMFPNAPYL bound to an HLA-A2 class I molecule the instant specification gives no guidance or direction as to other cancer antigens that can be bound by the claimed TCR. Thus, the instant specification does not establish possession of the genus of polynucleotides encoding "alpha/beta chain portion" or "single chain TCR" recited in the instant claims that bind to the genus of cancer antigens.

Applicant has not described the claimed invention sufficiently to show they had possession of the claimed genus of polynucleotides encoding "alpha/beta chain portion" or "single chain TCR" recited in the instant claims that bind to the genus of cancer antigens.

According to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, especially page 1106 3rd column, the written description

requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

What constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus. See, MPEP 2163 II.A.3a.ii.

Applicant is directed to the Revised Guidelines for the Examination of Patent Applications Under the 35 U.S.C.112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No.4, pages 1099-1111, Friday January 5, 2001).

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ZACHARY SKELDING whose telephone number is (571)272-9033. The examiner can normally be reached on Monday - Friday 8:00 a.m. - 5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Zachary Skelding/
Examiner, Art Unit 1644

.